NeurOnAir Podcast

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Transcript of Episode 5

Guest: Dr. Zoe Donaldson

Time Stamps:
00:00 - Intro
02:54 - Dr. Donaldson's research questions at a broad level
04:35 - Are humans truly monogamous? Social and genetic monogamy
08:19 - The story of how Dr. Donaldson decided to study this topic
11:22 - Studying unconventional model organism
14:33 - The role of neurotransmitters in bonding behavior
18:50 - Dr. Donaldson's finding about "approach cells" in the brain
22:31 - Can we execute the concept of the Eternal Sunshine of the Spotless Mind?
25:12 - How Dr. Donaldson's research relates to complicated grief, and management of anxiety & depression
27:35 - The differences between how humans and animals experience grief
34:35 - Social buffering
39:56 - How Dr. Donaldson's research could contribute to human life or treating mental illnesses
42:24 - Outro and Summary

Joanna Krzyśpiak: Over the last few decades, distances between us around the world have been compressed through air travel and technological innovations, but the pandemic has temporarily re-expanded the Earth. As we have been tasked with forcibly isolating from one another for the benefit of humanity, it's becoming evident just how difficult this is. Despite our digital-aged communication tools that were only found in fairytales not long ago, they never quite replace a real-life bond. So why do humans crave such a connection? Why are they so important to our well-being? In today's episode, we sit down with Dr. Zoe Donaldson, an Assistant Professor at the University of Colorado Boulder. There, she studies monogamous prairie voles to identify the neural and genetic basis of complex social behaviors, including social bond formation and the response to loss. Her findings could help us to better manage our physical and mental health, by uncovering the genetics of monogamy related behaviors, as well as the mechanisms of social buffering. In our interview, we discuss why she chose the prairie vole for her investigations, the neurotransmitters involved in bond formation, and why we do better getting through stressful situations together.

Şeydanur Tıkır: You are listening to NeurOnAir, brought to you by the next generation of neuroscientists at Albert Einstein College of Medicine in New York. We are your hosts today, two graduate students in Neuroscience.

Joanna Krzyśpiak: I am Joanna Krzyśpiak.

Şeydanur Tıkır: I am Şeydanur Tıkır.

Şeydanur Tıkır: Dr. Donaldson, thank you so much for being our guest today. It was a wonderful experience to listen to your talk as a part of our weekly seminars at Einstein. And now I feel lucky that we have you back here for a podcast episode. Although it's nice to be recording this online, I wish we were able to do it in person in New York, and I'm pretty sure there are things that you miss from New York City, right?

Dr. Zoe Donaldson: I would love to do some karaoke and some K Town small rooms with friends and I would love a real bagel. We don't have those here.

Şeydanur Tıkır: Yeah, you know, bagel is the one that I hear very often. Even one of my most recent Airbnb hosts was asking me to bring her a bagel from New York when I asked her if she wants anything.

Joanna Krzyśpiak: So I heard that it's something about the water in the bagels that makes it different. Do you know what the secret sauce is?

Dr. Zoe Donaldson: I don't know what the secret sauce is, but I do know that almost all the bagels here are not as chewy. And they insist on putting like fennel on the everything bagels, and they call them, Italian, not everything. It's just terrible, terrible travesty.

Joanna Krzyśpiak: Oh fennel, you know we always get it in our community share like the you know the vegetables. And my friend and I get it, and then we always fight over who's not going to get the fennel.

Şeydanur Tıkır: Yeah, although we enjoy it less often than usual, due to the covid pandemic, it's nice to have these amazing food opportunities in New York. So I wanna start talking about your research. You are studying a very intriguing topic. I think one of mankind's most interesting impulse is love, right, and making bonds with each other. At the broadest level, what are the questions about bonds that you're trying to answer through your research?

Dr. Zoe Donaldson: So I like one of the words that you use, which is impulse, because you know, we don't tend to think about this this much, but we have the ability to fall in love without actually having to learn to do so. Right. So it's an innate behavior for us. And it turns out that it's an innate behavior or there are some version of this that other animals also do innately. And so that's what I study. We use a species called prairie voles which are a small monogamous rodent that exists within the Midwestern states of the US. And these animals like us will pair up and raise their offspring together. And so they

display many of the same traits that we do when we form pair bonds, which is preferring to spend time with our partners, getting a little bit suspicious or even aggressive about potential meeting partners for our partner, we might call it jealousy, as well as biparental care of offspring. And so my lab is really interested in understanding what's special about the brains of these animals that enables them to be able to form these bonds. But bonds are dynamic, they can change over time. And so we're not just interested in sort of how do you form a bond, but what are the mechanisms from a neurobiological standpoint that enable the maintenance of these bonds over time, and how when we lose a partner, do you overcome that loss, and reach a point where you can go on with life.

Joanna Krzyśpiak: So I had kind of a follow up question out of my own curiosity. So in your talk you mentioned that voles were pretty monogamous, right, and pretty strictly so, and then trying to study you know how those pathways might kind of correlate to humans. But I mean, are humans truly monogamous, and can you make that comparison?

Dr. Zoe Donaldson: So one of my colleagues likes to say that prairie voles are a better model than we think because they do actually cheat on each other. And so this is a distinction that scientists have made for a very long time, that when we talk about monogamy for prairie voles and for humans as well we typically talk about social monogamy which is different from genetic monogamy. So genetic monogamy is when you're completely faithful and nobody cheats on each other. Of all the monogamous species that exist a very small subset are actually genetically monogamous, and these include things like we think coyotes based on the evidence that we have are actually genetically monogamous. For the majority of monogamous species they fall into this category of social monogamy. And so this basically means there's another individual that you're bonded with, you share resources, and you share care of the offspring, or as I often put it when I'm teaching, it's all about who you go home to at the end of the day, and less so about whether or not you're cheating on them. And so that sort of categorization applies to both humans and to prairie voles. And what we're interested in is not so much whether or not you cheat, but what's the glue that sort of helps to bond us over time that essentially makes it that you want to go home at the end of the day to be with your partner.

Joanna Krzyśpiak: I would just wanted to ask about genetic monogamy. I had not heard about that term before. Can you talk a little bit about that?

Dr. Zoe Donaldson: Genetic monogamy simply means that that pairs are faithful to each other. So the way that they assess this is by looking at offspring. Right. And so we know even in human populations that there's a subset of children that are sired by men that are not the father that's in the home. This is one of my favorite stories actually about just how we wound up with genetic testing more generally. Right, because it was a bunch of bird researchers who wanted to know how much monogamous birds actually cheat on each other. And so they developed DNA fingerprinting to get the answer to that question. And that same technology is what, then, is now used to determine whether or not suspects committed a crime, as well as just paternity testing in any species including humans. So the difference is just essentially that even in prairie voles we have something like 10 to 30% of offspring are sired by males that are not the partner that sharing the territory and helping to raise the offspring. There are

huge differences amongst male voles. So some are faithful and some are not. And there is an entire line of research on sort of what it, what is it, what are the biological mechanisms that leads to these differences in fidelity in voles, and then also a more evolutionary question of why is cheating maintained within these populations. Yeah, so it's simply, it's a scientific distinction in both instances you see monogamy manifesting as, who do you go home to at the end of the day in which offspring do you take care of. But in the case of genetic monogamy, those offspring are definitely yours, because there's no cheating happening.

Joanna Krzyśpiak: I see okay, cuz I hear genetic monogamy and I'm like, what's the gene?

Dr. Zoe Donaldson: It just basically means all the genes and your offspring came from the dad who is

Joanna Krzyśpiak: I'm sure I'm sure many of women who were cheated on are collectively disappointed. And men!, And men who were also cheated on they can't nail down the perp.

Dr. Zoe Donaldson: It's true. We don't really have very good like genetic testing to predict whether or not your partner is gonna cheat on you yet.

Joanna Krzyśpiak: So how did you decide to study this topic. What got you interested?

Dr. Zoe Donaldson: So I was actually an undergraduate at UCLA, and they had a field biology quarter, and I thought I wanted to study, you know, field biology and some sort of really cool tropical setting or equivalent. And I went to Nicaragua, where I was studying a harvest and species. You might also know them. They're called daddy long legs. I'm sure you've, you've seen them around. But this particular

Joanna Krzyśpiak: Unfortunately yes

Dr. Zoe Donaldson: They actually. So there's this whole myth, right, that these are the most poisonous animals in the world that they can't actually break your skin when they bite you - that's a total lie by the way. But they're there, by and large, they're called a pillar gannets that's the scientific name for them. They are part of the arachnid family, but that they actually are doing a good job of helping to eat up other smaller bugs. And so, so they're not really a pest species or anything. These guys that lived in Nicaragua would form these aggregations on spiny palm trees. And they would only be there during the day, during the night, they would go out and forage. And so there were some really obvious hypotheses. Like, why do they only used by the palm trees when they aggregate. And they have these really long limbs, so they could navigate over the spines. And so, this led to the idea that maybe they they were protected from predators, say like lizards that couldn't navigate the spines. And so there were a lot of questions that we were able to answer while I was there, including doing things like shaving the spines off the spiny palm trees to see if they use the sites less, and then starting to get into the question of how they found these aggregation. So there wasn't an, a one to one ratio between aggregations and spiny pumps, they only use a subset. And so the question was, then how do they find these sites if they all leave at night, then they have to come back to the same sites, do they just remember where they were,

or is there some sort of chemical cue. And so as I was answering these sort of broader questions about how they found each other, I became very interested in why they wanted to hang out with each other. And so it started out as this just inkling of an idea that what I really wanted to understand was not so much sort of the ecology, or the behavioral ecology underlying sociality, but rather sort of the mechanisms from a genetic and neuroscientific standpoint and I actually transitioned from working on bugs which is not a scientific term by the way to working on mammals when I was in grad school. And grad school is when I first met the prairie voles and they were just this fantastic model because they display these behaviors that are very reminiscent of what we display and what we experience as humans. And they are a set of behaviors, a suite of behaviors that we can easily study using common laboratory animals like mice and rats.

Şeydanur Tıkır: I love that story a lot, hearing about the chain of all the events that led you to your research question. And from there you ended up finding a fantastic model for your question, the voles, and studying it. So it's an unconventional model but you were able to find all the genetic tools that you need for your experiments. I'm pretty sure there have been some challenges getting throughout all this, but in general, how was the process for you? Was it easy to adapt your research to voles? And if people are interested in studying a species that's not a common model in science, would you recommend this to them?

Dr. Zoe Donaldson: So, this the answer to this question actually goes all the way back to my experience in Nicaragua as well. Because the course structure was that we spent about three weeks doing classroom learning before we went to Nicaragua, where we were undertaking these independent projects that we then wrote up and that was our grade for the semester. In those three weeks before we went to Nicaragua, they talked about how can you, what do you need to look for in order to be able to answer, realistically answer a question. And you know they highlighted that you might see one one Jaguar, maybe, if you're really lucky. Right. And like one Jaguar sighting does not an experiment make. And so I actually went to Nicaragua thinking you know what, I want a species that I can study that's really easy to find. Turns out, if you pick some species that aggregates always at the same places, that gets rid of all of the trouble of trying to find your animals to study them. And so those kind of big picture views have really informed how I've also proceeded. And so I think I mentioned, you can't study these behaviors in rats and mice. I would argue, if you can study something and mice, you should study it in mice, because the, the tools available from a generic perspective as well as just sort of the streamlining of everything that we have in terms of husbandry, behavior, etc., like, you should totally study it and mice. I'm interested in something that we can't study in mice. And so then the question becomes, you know what, what is the best model for studying something like pair bonding. And I would argue that the voles are actually a great model because we can employ a lot of what we know about mice and sort of transfer that knowledge over because they are another rodent and species. And so this is everything from husbandry, like we haven't faced significant challenges related to keeping these animals and getting them to breed within a laboratory setting. We can reinfuse our populations every few years by going out and trapping new animals from the wild and bringing them into the laboratory. And many of the molecular genetic tools that have been developed in the last few years, even things like optogenetics chemogenetics, the use of viral vectors, have transferred over reasonably well. Now it's

not 100% success rate, and there are challenges. But by and large, you know the rule of my lab is give it a try and it's sort of like a 75 to 90% chance that it will work. And within that, if it's on the lower end, maybe there's something we can do to modify the procedure to get it to work. And then there's just the 10% that for whatever reason, don't seem to work in voles. This is in contrast to if you picksay, coyotes, which are another great model of monogamy, there are a lot less tractable right. Now so doing optogenetics on a coyote is not going to be something that's going to be easy to do. But there are other questions that we can ask. So for instance, as a model of genetic monogamy, there may be things that we can learn from coyotes that we can't learn from say prairie voles.

Joanna Krzyśpiak: So some of your work has focused on linking the specific behaviors of these different species, so a lot of this pair bonding, to neurotransmitters such as oxytocin, vasopressin, and then serotonin. So you've done some amazing work on this link, not only in your own lab, but even, you know, back as a PhD student at postdoc in the past. And one of your goals has been to dissect the roles of these neurotransmitters in this bonding behavior. So can you tell us a little bit about what you have discovered so far, and what are some of the future research directions that this has opened up in your lab?

Dr. Zoe Donaldson: Yeah, so I think some of the most interesting things about. I'm going to focus on oxytocin and vasopressin but much of what I'll talk about is relevant in some ways to serotonin and other neurotransmitters as well. But oxytocin and vasopressin have been around for a really, really long time. Like, we can find versions of these, we would refer to them as hormones, but they can act in the brain where they can act as neurotransmitters. We can find them in worms, we can find sort of, a version in sponges. So they've been around forever, and whatever species, you look at the story that emerges is that these two hormones seem to be involved in social behavior in some way, if you inject a version of oxytocin into a female snail, she'll start laying eggs right. So she's involved in reproductive behavior. In C elegans it's involved in this telephoning behavior where the animals will actually twist around each other, which is associated with the C elegans version of mating. Because they're hermaphrodites it's more like one of them spears the other animal and that's how they mate when they don't just reproduce clonally. So I think I got off on a little bit of a tangent there. But basically, these, these hormones have been around every species we look at they're involved in social behavior. And so the question that I've been fascinated with is all those rules hold true until you get into the nitty gritty. And when you get into the nitty gritty, what you find is that the specific social behaviors that these hormones are involved in are very different. So if you infuse vasopressin into a male hamster, it will make them super aggressive and fight off everybody else. If you put it into a male prairie vole, it will make them want to form a bond with a partner. And so it has this diametrically opposed effects on aggression and affiliation in a species specific context. So how can this happen? Like what happens in the brain that leads to the same molecule being routinely involved in social behavior but producing vastly different outcomes in different species? And so much of my work focused on sort of how differences in where the receptor for this molecule might be localized in the brain to mediate these different effects on behavior. And so what I think is really cool about this is if you take the perspective of focusing on the receptor, if you just think of these hormones as sort of bathing the brain, then the receptor can act as sort of this translator of sorts. When you express it in one part of the brain, say part

of the hypothalamus, and you activate that receptor, it may trigger aggressive behavior because of the downstream pathways that are activated within the brain. Whereas if you express it and say the ventral pallidum, where it is in male prairie voles, then when you activate it, you may wind up activating reward and motivation related behaviors that lead to the formation of a bond. And so I think what it really does is it highlights the complexity of gene expression within the brain and also provides us with an evolutionary mechanism where changing the expression pattern of a single gene say the vasopressin receptor can lead to both individual differences in behavior within a species, but also these vast differences and social behavior that we routinely observe across species.

Joanna Krzyśpiak: Interesting. So it's not it's not as simple as, you know, genes to neurons to behavior. There's all this kind of interplay in between, and then the location, and the other things involved that then lead to these behavioral differences, not only within the animal, but then just between different sexes of the animal and things like that.

Dr. Zoe Donaldson: Absolutely. So, I mean, there's a big push to move away from just grinding up an entire brain. Because, while, the liver may be a relatively homogenous organ, the brain is not and we lose that complexity if we start thinking of the brain as just a single homogenous organ.

Şeydanur Tıkır: You also had some beautiful calcium imaging studies that you're done recently where you define some neural ensembles, or group of neurons, that are firing only when the partner is approaching towards the animal. Could you please briefly tell about what your finding was? And also, does these so called approach cells encode the identity of the partner as well?

Dr. Zoe Donaldson: Sure. So just for a little bit of background on this, prairie voles have historically been a neuro endocrine model. So they were adopted by endocrinologists to better understand the hormonal basis of behavior. And when I started my laboratory based on some of what I had learned as a postdoc technically was a realization that with the molecular genetic tools that have been developed in the last decade or so, we could actually use this model, and we could look at pair bonding from a new perspective. And so in my lab here we've implemented in vivo calcium imaging and variables which allows us to visualize neuronal activity occurring in real time with single cell resolution. And so in the work that I presented when I gave my talk, one of the things that we've been able to do is to identify a subset of cells within the nucleus accumbens, and this is a brain region where we know that oxytocin and dopamine signaling is required for pair bond formation within prairie voles is to actually look at, you know, is there a signature of neuronal activity that corresponds with bond formation and differentiates between when they're interacting with their partner versus a novel individual opposite sex and individual. And so what we recently published was that there's a subset of neurons or an ensemble of neurons that predict approach to different social stimuli, either towards their partner or towards a novel individual and one of the things that we did after we identified this ensembles, we just sort of looked at what happened to it over time. So we started with animals that didn't have a bond, we were able to identify ensembles that were specific for say two different opposite sex individuals. And then we pair them with one of those individuals. And what we found is that upon pairing, they mated, they formed a bond. But that this cell population that signaled approach to that individual actually expanded in size. So

we can almost think of this as a reallocation of neurons to signaling partner approach within these animals. Once we had identified these neurons, we then were able to ask. We had separately sort of identified partner approach neurons and novel approach neurons. And we wanted to know, are these distinct populations or have we just identified cells that you know signal approach social approach more generally. And we found that these two populations were actually distinct from each other. They were no more overlapping than you would expect by chance. And so one potential interpretation of this is that it is encoding something about the identity of the individual. So it's got some specificity that also includes information about not just whether they're approaching or the decision to approach, but who they're approaching.

Şeydanur Tıkır: Interesting. It could also be getting projections about the identity from another region in the brain, right? Do you have any alternative hypotheses about that?

Dr. Zoe Donaldson: So that's our working hypothesis. And we sort of have two brain regions that are the most likely players in this. So the ventral hippocampus has been implicated in at least memory formation for social memories and we know that that directly integrates the nucleus accumbens shell. And so that's one likely key player. Is that the ventral hippocampus may be sending information about "who" to the nucleus accumbens. And then the other likely players the medial prefrontal cortex, which I think is involved in the more complex sort of associations that are taking place in bonding and may also be the seat of sort of social memory at the longer term phases of the bond. And I think that that could be a second source of input that's providing some specificity for this signal.

Joanna Krzyśpiak: So because it's it's a little decentralized, then, does that mean that the Eternal Sunshine of the Spotless Mind concept cannot actually be executed, or or is that, you know, maybe in our future?

Dr. Zoe Donaldson: So I have a grant application that I referred to as my Eternal Sunshine of the Spotless Mind. But I do think that these sort of networks of neurons are encoding different facets of bonds, which include the identity of the individual that you're bonded to, the memory of past events, the valence, so whether or not it's good or bad, right, the saliency how important this is, are probably distributed across a network of brain regions that are implicated in social behavior, ranging from the hippocampus to the amygdala, the mesolimbic dopamine system, which includes the nucleus accumbens, the prefrontal cortex. The prefrontal cortex is not part of that, but it's another brain region involved. So my working hypothesis is that these different brain regions are important for different aspects of this. And so if you want to completely obliterate the memory of that individual, it may be possible. For instance, if you can just erase the identity information, then you might wind up in almost an Eternal Sunshine of the Spotless Mind scenario where you don't remember the bond, but you have all these ancillary things that are happening right so in prairie voles, not only do they show selective affiliation for a partner, but they're aggressive towards everyone else. And I would anticipate that if you could erase the memory of the partner just who their identity is, it would just lead to a state of confusion, where they still want to be aggressive towards everyone else, they just don't really know why - if I was being overly anthropomorphic. And so we've actually started thinking instead about how we

could maybe uncouple sort of the feelings or the emotional saliency of the bond from the identity. So rather than just like eliminating social recognition or social memory, can we just uncouple by say erase the feeling of love, if you will, from that memory. And we think maybe by targeting brain regions like the nucleus accumbens that will be essentially erasing some of the motivation and some of the reward associated with that individual. So it's not that they wouldn't remember them anymore that maybe they don't have the same strong emotional reaction to that individual.

Joanna Krzyśpiak: Sounds like a tough complex problem to nail those a certain, I guess, neuronal bonds, right, all those different synapses. So, you know, very often -kind of going off of this Eternal Sunshine of the Spotless Mind scenario, you know- very often in life, we also need to cope with changes and ongoing bonds, so such as the loss of a loved one. Or, you know, redefining a relationship as basically you know this this procedure. My in theory do or losing contact with friends and family after a move to a new city. So some people have more difficulty in managing these changes than others, resulting in what is often referred to as adjustment disorder. So could your research potentially help understand and manage the anxiety and depression that comes with this, and if so, how, how might that be involved?

Dr. Zoe Donaldson: So that's exactly where we're headed. We're focused specifically on complicated grief. So these are individuals where they lose someone. And for most people, there's sort of a recovery process or adaptation, if you will, that takes place. People who go through this sort of talk about how a lot of the transition involves moving the memories of that individual from being painful to being bitter sweet. And so we have a terminology for this and how we talk about it. But what we don't know is what has to happen in the brain, in order for that adaptive process to take place, in order for people to incorporate the finality of the loss. And there's a subset of individuals who seem to struggle with this, who become mired in that initial chronic, or sorry, acute stage of grief and it manifests in a chronic fashion. So how can we stimulate those processes for people that are having trouble moving on. And right now we have some some cognitive behavioral therapies that actually work pretty well for this. In particular, it's called complicated grief therapy. It's distinctly different from other forms of cognitive behavioral therapy. But what we don't have is any sort of pharmacological intervention that can help with this. And so they have tried SSRIs, Citalopram in particular, and while that alleviates some of the depression related symptoms, the sadness, etc., it doesn't alleviate the core symptoms of grief, which really focus on the loss of a particular individual, and the yearning for that individual. And so the hope is by better understanding sort of how this adaptive process occurs in say a vole, we might gain insight into specific either aspects of neural circuits or cell populations within the brain that can be pharmacologically targeted in order to enhance the effects of a complicated grief therapy.

Şeydanur Tıkır: Along these lines, you know, I was thinking that just as the name implies, you know the name of complicated grief, human beings experience the grief in a very complicated ways and also in different ways, right. I see a lot of different responses that people give upon losing their loved ones. Although some of them can handle it very well, some people like they can present some Freudian suppression mechanisms, try to find something to blame or someone to blame for the loss. You know, they're all different kinds of reactions. On the other hand, animals don't have such complicated, I think, cognitive or subconscious mechanisms. Right. And I think from maybe an evolutionary perspective they

are also a little bit more used to losing their partners. I'm not very sure if what I'm saying is correct, but in the wild, often their partners leave and then they've been caught by a predator I feel like they should be more used to this right? So do you think that there are huge gaps between animals and humans, and how they experience grief? And are there ways that we can fill these gaps?

Dr. Zoe Donaldson: I think that this is a really interesting question, and to some extent, the idea of animal grief and the extent to which it mirrors human processes remains largely unexplored. You know, there's sort of popular press books about single incidences in which animals have expressed what we believe to be a form of grieving. So there was a sort of very popular example of this a few years ago where a female orca gave birth and her offspring was dead, and she kept raising it to the surface for days on end, despite the fact that it had died. We talked about elephants displaying what we consider to be a form of grieving, or you know, dogs, when when they've grown up together and one dies and the other one stays behind displaying sort of symptoms that seemed to mirror depression. What I would say is, you know, first of all, I want to be clear that when I use the term complicated grief. This is a medical term. So it's not referring to the complexity of the grief reaction. But rather to the medical term of complicated, so complication of a medical process or biological process, and that's the origin of this term is purely sort of how clinicians talk about disease severity or the or the complexity of the disease process, if you will. And it's not to be confused with the fact that grief is inherently a sort of very diverse and complex process that's influenced, not only by biological factors, but also by sort of cultural factors. And this is evident in different cultures have articulated that there are different ways we quote unquote should grieve. And we also see that grieving manifests individually in very different ways. There is no right way to grieve and there is no straight line trajectory from loss to recovery or loss to adaptation. What I will say is that, you know, no, I don't think that prairie voles display the same complexity that we do as human beings. I mean, even their social world is not as complex as ours. Right. Like, I can't imagine a prairie vole being a frienemy, for instance, that's a pretty complex and human specific. I could imagine some monkeys that might have frienemies, but I don't think the voles do. But if you think about sort of core emotions and core emotional traits that have been studied and animals, we have learned a lot about basic underlying emotional traits from studying less complex models such as rats and mice and applying what we've learned to humans. So a good example of this might be fear and anxiety. So in humans, our day to day anxiety probably comes less from the likelihood of being eaten by a lion or a hawk or whatever, and more from the world that we have created right. So we have anxiety about, you know, our jobs, our performance, our livelihoods, which are really these constructs that don't apply to animals right. Yet what we have learned about the basic underlying structure of anxiety using these organisms has proven fruitful for developing therapies that help with the more complex sources of anxiety for humans, because ultimately these things have shared underlying neurobiology and circuitry. And so I think that to a large extent, this is also true for a loss in animal models and for humans. So well, while the trajectory of recovery in voles may be more biologically driven and less, you know, reading self help books or other forms of support that humans may engage in that the underlying processes are shared, and therefore we can gain insight into what might be going on. For individuals who are grieving or suffering from loss.

Şeydanur Tıkır: Yeah, that makes sense. I'm actually quite surprised how well the model is. And I actually didn't know that they can cheat as well. I just learned it from you.

Dr. Zoe Donaldson: Yeah, I think that colloquial use of monogamy implies that we don't cheat, but it actually has more to do with the structure of our family units than anything else.

Joanna Krzyśpiak: Yeah, no, I mean, and you know, as we said that does make sense, even though we don't have the immediate threat of some other kind of species attacking us, or or killing us off, the responses are very similar, right. You still interpret things as a threat, you still care for basically the same things, you know, resources, you know, trying to provide for your family. Most of the wars I think they say are started based off of access to resources, you know, so these are very primal things that, you know, we've overlaid all these complicated societal norms and patterns onto, but it kind of boils down to very similar circuitry. Yeah.

Dr. Zoe Donaldson: And I think the other way in which it's shared is that if you think about if you think about human bonds or vole bonds, there are biological mechanisms that are in place to sort of cement these bonds over time. Right. And so, so we use approach behavior in our testing because we reason that if you don't, if you don't want to approach your partner reunite with your partner, then you can't maintain that bond. There's nothing to glue it together over time. And the same is true for us, like if we don't want to physically be with our partners, then there's a pretty good chance that like the relationship is not going to survive. Right. And if you think of what loss is, loss is just basically all of the systems that are in place that are motivating you to be with that individual now go unrequited. And so if you think in those terms, it's really similar for us and for a vole. You have a drive to be with someone and that drive is frustrated because it can't be met.

Joanna Krzyśpiak: So some of these stressors. You seem to have also included in some of your studies. So for example, the phenomenon of social buffering. And you mentioned an example I believe, in one of your, your papers about how children through World War 2 had processed the take over differently depending on whether or not they were present with family or not. And that this concept of social buffering seemed to alleviate some of that that stress and then the kind of the long term outcome of it. So could you tell us a little bit more about what that is and potentially, you know how understanding this might influence certain therapies, maybe you know company behavioral therapy or anything like that in the future?

Dr. Zoe Donaldson: Yeah, absolutely. So social buffering is actually a phenomenon you see across pretty much every single social animal species. So it's documented in laboratory studies and pigs in guinea pigs in rats and mice in primates. Basically, if you're a social animal, then you probably exhibit some form of social buffering, which is basically to say that if there are other species members around then that will decrease your sort of vigilance behaviors, your anxiety levels, maybe your fear levels, etc. And this is particularly powerful in humans. Right, so we see this manifest really really strongly when you're talking about toddlers who display a lot of stranger danger when their moms around, it's a lot less stressful, or their dads, for that matter, but some trusted figure. The difference between humans and say just any

other social species is that it really does matter who that support figure is right so for a three year old human it can't just be any adult it matters if it's a parent in terms of having the stress-reducing effect. So the work that we've done on social buffering of fear responses is actually work that was done in mice, where we can show that if another mouse is present that they show reduced levels of anxiety and reduced levels of fear. So this has myriad implications. Right. I mean it explained so many things, why you feel less stressed out, if you have someone that you can share a traumatic experience with. Why our first initial reaction typically when we experienced a traumatic event is to go to someone who can console us who we trust to help us through this sort of emotional journey. It probably also contributes to the repeated effect that we see of having a strong social support network so even people who are recovering from surgery report lower pain levels if they have a close social support figure they're holding hands with them. People recover are more likely to recover from cancer, stroke, heart attack, substance use. I mean, you name it. If you have a strong supportive social network, your chances of recovery are better. And I imagine that some portion of that is buffering of the stress of going through that event, whether it be a physiological or mentally taxing experience.

Joanna Krzyśpiak: Are people flooding your inbox with advice for how to get through COVID isolation?

Dr. Zoe Donaldson: I wish I had really good advice on how to get through COVID isolation, because we actually taught a course here at CU Boulder. That was pretty novel like it goes a one credit course it's open to the community as well as to two students here where they drew on different professors who had different expertise in different areas of the pandemic. So they had neurologists who talked about COVID, and they but they had me and a couple of psychologists who talked about sort of the stress of isolation and everything that we're going through, and how do you, how do you combat loneliness and what do you do when all of your attachment relationships are disrupted and your normal sources of social reward are not available to you. And unfortunately, there isn't a great answer to this question except you know my exercise schedule was also disrupted by COVID. Do the best you can.

Joanna Krzyśpiak: Until you and your lab figure it out. Right. So...

Dr. Zoe Donaldson: Yeah. We'll keep working on it. But I think we do need to be careful and thinking about, you know, drugging these things away.

Joanna Krzyśpiak: Yeah I mean my first thought was, you know something in between where, for example, you could use a feedback mechanism like an EEG or an fMRI and perhaps if you could look up the certain regions that you know were involved in this, then use some kind of cognitive behavioral therapy to try and stimulate those regions or destimulate them you know through your own kind of thought processes rather than than just drugging it. That was kind of my...

Dr. Zoe Donaldson: Yeah I agree. And there's a lot of behavioral interventions that we can use. Right. So one thing I do a lot with friends, is we just set up writing hours. And even though it's literally the two of us sitting there writing on our separate computers as we have our zoom portals open, and it creates a sense of accountability, but also a sense of shared experience. You know, like everyone I have various

assorted ways of linking up with friends and I would say the upside of all of this has been that it has reinforced relationships that are more geographically distant because it doesn't matter anymore. Right.

Joanna Krzyśpiak: Yeah, but that that mental barrier has been taken down, even though it's been available for years it's finally become a norm. Yeah.

Şeydanur Tıkır: So speaking of these behavioral interventions like social buffering, I'm also interested in hearing from you what are the ways that you see your research contributing to human life or treating mental illnesses in the future.

Dr. Zoe Donaldson: So I think the first level of this is just awareness. And I think, in particular, awareness about grief, the processes that are required to adapt to a loss and the fact that it is not a linear trajectory and it's not the same for everybody is just a good starting point. So when I was teaching in this course about COVID 19 here, I had one student who who said it was just reassuring to find out that loneliness is actually a biological state of deprivation. But it is not an ephemeral thing and it's an actual need that we have. And when just like when you're hungry or thirsty, loneliness is your body or your mind telling you that you have an unmet need. And so I think there's a lot to be gained just from from bringing this idea to the forefront that like we have needs that are beyond just our physical needs. And now we have a model that we can use to try to better understand what does that representation of need actually look like within the brain because if we can understand that, then we can start talking about next steps. And so I would say like next steps for me are thinking about ways in which we could either incorporate some of what we learn about basic underlying learning and reward processes potentially into therapeutics that already exists, like complicated grief therapy, but ultimately also to come up with pharmacological tools that can help people on their journey to recovery from loss of a loved one.

Şeydanur Tıkır: This is beautiful. And I think that sounds very impactful. There are also a lot of different disorders that has over attachment or under attachment or like there is these abusive bonds, right, there are a lot of different ways where bonds could be trouble in human life. Do you think that in the future, we could make some models for these diseases as well?

Dr. Zoe Donaldson: Yes, and I think ultimately some of the underlying processes are going to be shared. Right. So I think ultimately complicated grief is a form of over attachment. It's an inability to move on from an attachment and that we see that similar sort of over emphasis on a particular attachment over attachment and other disorders such as separation anxiety disorders. And so I'm hopeful that what we learn will be able to be applied more broadly, and that it may even give us some insight into the flip side of the coin, which is under attachment, which we see occurring and schizophrenia and depression and to some extent, maybe in autistic individuals.

Şeydanur Tıkır: Sounds very interesting. It was awesome to have you today thank you so much for your time. We didn't have a chance to talk about any of your recent studies on population level coding

although we discussed some calcium imaging studies on single cells, but hopefully maybe we will recruit you back later in a few years, and hear about new discoveries as well.

Dr. Zoe Donaldson: That would be great. Thank you for the opportunity. I think it’s awesome that you guys are doing this podcast.

Joanna Krzyśpiak: Yeah next time you're in New York hopefully in post pandemic times maybe hit up a karaoke bar and...

Dr. Zoe Donaldson: And grab a bagel afterwards?

Şeydanur Tıkır: Yeah, and grab a bagel!

Şeydanur Tıkır: Prairie voles and humans share pair bonding similarities such as raising their offspring together, and even getting a little bit suspicious or aggressive about the threat of competing mating partners for our companion. Dr. Donaldson's lab is exploring how the brains of these animals enable them to form and maintain these bonds, and how what we learn from them can inform what happens within our own minds when we lose a partner, and must deal with overcoming that loss to go on with life.

Joanna Krzyśpiak: But wait, are humans really monogamous? And are monogamous voles a good model for us? Turns out that although voles are known to be monogamous, this type of monogamy is actually called social monogamy, which is more about sharing resources and care of the offspring, and less so about whether or not you're cheating on them. This is different from genetic monogamy where you're completely faithful and nobody cheats on each other. As Dr. Donaldson says, that bond is what makes us want to go home to our partner at the end of the day, regardless of what other types of bonds might be happening!

Şeydanur Tıkır: Through the use of in vivo calcium imaging, her lab has identified a subset of cells within the nucleus accumbens that serves as a signature of neuronal activity that corresponds to bond formation, and differentiates between partner interactions versus a novel individual. Although this region uses oxytocin and dopamine signaling for pair bond formation, the type of cells involved is a key factor, and it’s not always the same across species! For those who have seen the movie Eternal Sunshine of the Spotless Mind, you may wonder whether it would be possible to erase the memory of a partner from the brain. Dr. Donaldson says that due to the mechanisms and networks involved in pair bonding, erasing the identity of the partner may be less effective than uncoupling the feeling of love from the identity. That may happen by targeting brain regions like the nucleus accumbens, but don’t toss those tissue boxes away just yet, we still have a lot to learn about how to induce such a detachment in humans! A closer target for us to learn how to manage better is complicated grief, a process of long lasting painful emotions that some people have difficulty moving on from after losing a loved one.

Understanding the neural mechanisms that enable this transition could lead to discovery of new therapies for grief, and also potentially help understand and manage anxiety and depression.

Joanna Krzyśpiak: The prairie vole model has enabled Dr. Donaldson's lab to understand pair bonding from a new perspective to lead to novel discoveries, and highlights the importance of choosing the right model organism for your question, even if it's an unconventional one.

Şeydanur Tıkır: Your hosts for this episode were Şeydanur and Joanna. Thanks for joining us today! Visit our website neuronair.org for more resources about today's episode and our guest Dr. Zoe Donaldson. You can visit her website at www.zdonaldsonlab.com and find her on Twitter @DrZoePhD. You can also follow us on social media @neuronaircast to leave comments on today's episode, or to get in touch with us directly, email us at neuronairpodcast@gmail.com. And finally, if you enjoyed the episode, please subscribe, and review us! See you next time!